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(57) Abstract

The invention relates to γ-butyrobetaine and 3-(2,2,2-trimethylhydrazinium) propionate (Mildronate)-containing pharmaceutical compositions for oral, parenteral, subcutaneous or rectal administration for the treatment of heart-blood vessel diseases of various genesis and localization, blood circulation disturbances, stenocardia, myocardium infarction, arrhythmia, hypertension, myocarditis and low cardiac potency. This composition in the experiments on anaesthetized cats at a dose of 5 mg/kg of γ-butyrobetaine + 5 mg/kg of Mildronate, i.v. increases a total blood flow by 18 %, blood pressure and heart rhythm being practically unchanged. The composition arrests adrenaline-induced blood vessel spasms in isolated rabbit ear, in a concentration of 2.0 μM of γ-butyrobetaine + 2.0 μM of Mildronate, it decreases reperfusion pressure by 33 %. NO-synthase blocking essentially decreases the composition effect on adrenaline-induced blood vessel spasms. At a dose of 60 mg/kg of γ-butyrobetaine + 40 mg/kg of Mildronate, the composition by 70 % declines mouse lethality from $CaCl_2$-induced arrhythmia, and at a dose of 30 mg/kg of γ-butyrobetaine + 30 mg/kg of Mildronate, p.o. by 60 % decreases rat lethality from $CaCl_2$-induced arrhythmia. In the prophylactic and therapeutic regimens at a dose of 50 mg/kg of $(g)g-butyrobetaine + 50 mg/kg of Mildronate, the composition in the experiments on rats effectively prevents myocardium from occlusion-reperfusion-induced failures and ventricular fibrillations. In the comparative experiments the claimed composition demonstrates a more potent effect as compared with the known preparation Mildronate and γ-butyrobetaine effects if they are applied separately. The composition is notable for a low toxicity and wide interval of therapeutic action safety.

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PHARMACEUTICAL COMPOSITION FOR TREATING CARDIOVASCULAR DISEASES CONTAINING 3-(2,2,2-TRIMETHYLHYDRAZIMIUM) PROPIONATE AND GAMMA-BUTYROBETAINE

The invention relates to the pharmaceutical compositions, namely, to the pharmaceutical compositions for the treatment of such heart and blood vessel diseases, which are connected with blood circulation disturbances of various genesis and localization, stenocardia, myocardium infarction, arrhythmias, hypertension, myocarditis as well as low heart potency.

The proposed therapeutic composition contains known chemical substances, the use of which gives unexpected pharmacological effects. Namely, there is offered a pharmaceutical composition which contains γ–butyrobetaine in a combination with 3-(2,2,2-trimethyl-hydrazinium)propionate as an active principle and pharmaceutically acceptable fillers or solvents.

In the treatment of cardiovascular diseases 3-(2,2,2-trimethyl-hydrazinium)propionate is a known preparation (Mildronate, Quaterine) (UK patent GB 2105992), the mechanism of action of which is based on limitation of carnitine biosynthesis rate and related long-chain fatty acid transport limitation through mitochondria membranes (Simkhovich B.Z., Shutenko Z.V., Meirena D.V. et al. 3-(2,2,2-trimethylhydrazinium)-

propionate (THP) - a novel γ–butyrobetaine hydroxylase inhibitor with cardioprotective properties. Biochem.Pharmacol. 1988, 37, 195-202).

BACKGROUND ART

γ–Butyrobetaine (actinine), from which the mammalian organism synthesises carnitine, was primarily characterised as a toxic substance which accelerates respiration, causes salivation and lacrimation, pupil dilation, vasoconstriction and heart stop in diastole (W.Linneweh, Z.Physiol.Chem., 42, **181,** 1929). At the same time, in later papers other authors ascertained that γ–butyrobetaine is extremely low toxic (LD_{50} >7000 mg/kg, s.c.). (W.Rotzsch, I.Lorenz, E.Strack, Acta biol. med. ger. 1959,3,28-36).

Literature lacks the data on nonsubstituted γ–butyrobetaine cardiovascular effects, though it was reported (Hosein E.A., McLennan H. Pharmacological action of y-butyrobetaine. Nature, 1959, 183, 328-329) that γ–butyrobetaine is a substance similar to acetyl choline with a prolonged action. However, later the same authors reported that by an error the experiments involved, instead of γ–butyrobetaine, its methyl ester which in fact possesses cholinergic properties. Contrary to the former nonesterficated γ–butyrobetaine was characterised as a pharmacologically inert substance (E.A.Hosein, P.Proulx, Isolation and probable functions of betaine esters in brain metabolism, Nature, 1960, 187, 321-322. A.S.V.Burgen, F.Hobiger. Brit.J.Pharmacol., 4, 229 (1949), E.Strack, K.Foesterling. Z.Physiol.Chem., 1953, 295, 377).

γ–Butyrobetaine administration increases the level of carnitine biosynthesis in the organism serving as a substrate in this process. Thus, it

would be naturally to anticipate that in the organism at a simultaneous administration of carnitine biosynthesis blocker 3-(2,2,2-trimethyl-hydrazinium)propionate and γ–butyrobetaine the pharmacological effect of 3-(2,2,2-trimethylhydrazinium)propionate should decrease because carnitine biosynthesis is activated if γ–butyrobetaine concentration increases. On the contrary, we managed to unexpectedly discover that an opposite effect is observed, i.e. γ–butyrobetaine intensifies 3-(2,2,2-trimethylhydrazinium)-propionate effect on the cardiovascular system.

DISCLOSURE OF THE INVENTION

The experiments were performed on male and female (2.9-3.8kg) anaesthetized cats (urethane 200mg/kg and chloralose 50mg/kg, both i.p.). A chest was opened in the experimental animals, they were artificially respirated, and blood pressure in the carotid artery as well as general aorta blood flow were measured on physiograph DMP-46 "Narco Bio-Systems" USA.

It was detected that the pharmaceutical composition which contains γ–butyrobetaine combination with 3-(2,2,2-trimethylhydrazinium)-propionate possesses a marked effect on blood vessel tonus and blood circulation, which exceeds every separate active principle action, blood pressure decrease is not practically observed, while a total blood flow increases very considerably (Table I).

Table 1

3-(2,2,2-Trimethylhydrazinium)propionate (M), γ-butyrobetaine (GBB), acetyl choline (Ach) and the pharmaceutical composition effects on haemodynamics of anaesthetised cats

Substance	Dose, i.v. mg/kg	Blood pressure changes, %	Heart rate changes	Blood flow rate changes, %
M	5.0 10.0	± 3 ± 5	± 3 ± 3	+5 +8*)
GBB	5.0 10.0	±÷ 4 -7 ÷ +3	± 5 ± 5	6 12*)
M + GBB	5.0 + 5.0	-7 ÷ +3	± 5	+ 18*)**)
Ach	0.001	-35*)**)	-20*)**)	± 8

*) $p<0.05$ in comparison with the initial data
**) $p<0.05$ in comparison with GBB and M groups

If this effect were connected with earlier incorrectly postulated cholinergic component, which mainly relates to γ–butyrobetaine ester (The Merck Index, Eleventh Edition, 1871) impurities in the samples of insufficiently purified γ–butyrobetaine, then one would anticipate a significant decrease in the blood pressure. On the contrary, such a cardiovascular effect indicates a positive inotropic effect of the proposed therapeutic composition with simultaneous decrease in peripheral resistance according to an absolutely different mechanism, which can be applied in the treatment of low heart potency and blood circulation failures of various genesis.

The pharmaceutical composition containing γ–butyrobetaine also by 2-3 times more potently affects adrenaline-induced blood vessel spasms in isolated rabbit ear than the known preparation 3-(2,2,2-trimethylhydrazinium)propionate (Table 2).

Table 2

3-(2,2,2-Trimethylhydrazinium)propionate (M) and γ-butyrobetaine (GBB) effects on adrenaline-induced isolated rabbit ear blood vessel spasms

Substance, concentrat. (μM)	Perfusion pressure (mm Hg) max/min				Perfusion pressure decrease (%)
	Initial parameters		Final data (after adrenaline 3.10^{-7}M addition		
	max	min	max	min	
M, 0.3	38±5	8±2	125	80	1
M, 1.0	38±5	8±2	123	77	4
M, 2.0	38±5	8±2	126	80	8*
GBB, 0.3	38±5	8±2	124	76	6
GBB, 1.0	38±5	8±2	125	80	15*)
GBB, 2.0	38±5	8±2	125	78	18**)
M+GBB, (1.0+1.0)	38±5	8±2	125	78	22**)
M+GBB, (2.0+2.0)	38±5	8±2	126	80	33**)***)

*) $p<0.05$ against the control
**) $p<0.01$ against the control
***) $p<0.05$ against GBB and M groups

In the same way it unexpectedly turned out that together these both substances in one pharmaceutical composition act synergically causing a further spasmolytic effect intensification.

Moreover, it unexpectedly was noted that the basis of this vasodilating effect is NO-synthase activation, which cannot be completely blocked even by L-NO_2-arginine if a composition of 3-(2,2,2-trimethylhydrazinium)propionate and γ–butyrobetaine is used (Table 3*.

Table 3

3-(2,2,2-Trimethylhydrazinium)propionate (M) and γ-butyrobetaine (GBB) and their pharmaceutical combination effects on adrenaline-induced rabbit ear blood vessel spasm in the presence of L-nitroarginine (L-NO_2-Arg) (10mg/l)

Substance concentrat. (μM)	Perfusion pressure (mm Hg) max/min				Perfusion pressure decrease (%)
	Initial parameters		Final data (after adrenaline 3.10^{-7}M and L-NO_2Arg addition)		
	max	min	max	min	
M, 0.3	36±5	7±2	165	102	0
M, 1.0	36±5	7±2	163	100	0
M, 2.0	36±5	7±2	165	100	2
GBB, 0.3	35±5	8±2	168	105	0
GBB, 1.0	35±5	8±2	165	100	0
GBB, 2.0	35±5	8±2	163	100	0
M+GBB, (1.0+1.0)	35±5	8±2	165	100	3
M+GBB, (2.0+2.0)	35±5	8±2	163	98	6*)

*) $p<0.05$

Special experiments showed that the pharmaceutical composition on the basis of γ–butyrobetaine possesses also antiarrhythmic properties. Thus, in $CaCl_2$-induced arrhythmias in mice the pharmaceutical composition containing 50 and 100 mg/kg of γ–butyrobetaine demonstrated a statistically significant protection from lethal arrhythmia (in 30-40% cases). This experiment was performed on male and female conscious albino mice (19-26 g) administering to their tail vein 2% (by weight) calcium chloride solution, animal protection against lethal arrhythmia being used as an effect criterion (Table 4).

Table 4

3-(2,2,2-Trimethylhydrazinium)propionate (M), γ-butyrobetaine (GBB) and their combination effect on $CaCl_2$-induced lethal arrhythmias in mice

Substance	Dose, mg/kg, p.o.	The number of observations	Survive	Protection % against the control
M	8	10	2	10
	20	10	3	20
	30	10	4	30*
	50	10	4	30*
	100	10	5	40*
GBB	8	10	2	10
	20	10	1	0
	30	10	3	20
	50	10	5	40*
	100	10	4	30*
M+GBB	42+8	10	2	10
	33+16.5	10	6	50*
	30+20	10	5	40*
	25+25	10	6	50*
	20+30	10	7	60*
	16.5+33	10	7	60*
	10+40	10	3	20
	50+50	10	6	50*
	40+60	10	8	70*
	33+67	10	4	30*
Control	-	10	1	0
Quinidine	10	10	2	10
	30	10	4*	30*
	50	10	6*	50*
Etmozine	5	10	3	20
	10	10	5*	40*
	30	10	5*	40*

* $p<0.05$ against the control

γ–Butyrobetaine closest structural analog 3-(2,2,2-trimethyl-hydrazinium)propionate also possesses, as known, (UK patent GB 2105992) a similar antiarrhythmic efficacy. We discovered that the effect of both substances in a combination in the form of a pharmaceutical composition is higher than each substance has separately (Table 4),

exceeding that of the known antiarrhythmic agents Quinidine and Etmozine. We should note also a very low toxicity of the combination claimed compared with the control preparations.

Acute toxicity was studied on male and female albino mice (19-26 g), 10 animals in a group. The substances were administered as a 10% solution orally or i.v. (with 0.004 ml/sec rate). It was determined that at γ–butyrobetaine oral administration LD_{50}>4500 mg/kg, but at intravenous injection LD_{50}=1860 (1430-2418) mg/kg, which testifies that γ–butyrobetaine is a practically nontoxic agent.

At oral administration of γ-butyrobetaine and 3-(2,2,2-trimethyl-hydrazinium)propionate mixture (1:1 by weight) its LD_{50}>4500 mg/kg., and at i.v. injection LD_{50}=1750 (1434-2135) mg/kg. So, being used in a combination the toxicity of both substances has no synergic character.

Similar to mice, also in rats, applying a pharmaceutical composition containing 3-(2,2,2-trimethylhydrazinium)propionate and γ–butyrobetaine, in $CaCl_2$-induced arrhythmias there is observed a marked combination protective effect against lethal $CaCl_2$-induced arrhythmias (Table 5).

Table 5

3-(2,2,2-Trimethylhydrazinium)propionate (M), γ-butyrobetaine (GBB) and their combination effect on $CaCl_2$-induced lethal arrhythmias in rats

Substance	Dose, mg/kg, p.o.	The number of observations	Survive	Protection % against the control
M	10	5	1(20%)	15
	20	5	1(20%)	23
	30	5	1(20%)	25
GBB	10	5	1(20%)	20
	30	5	1(20%)	32
M+GBB	30+10	5	2(40%)	37
	30+20	5	1(20%)	35
	30+30	5	4(80%)	60*
	20+30	5	3(60%)	52*
Control	-	5	0	0
Quinidine	10	5	2(40%)	46
	3	5	1(20%)	25
Etmozine	3	5	1(10%)	20
	10	5	2(40%)	46*

* $p<0.05$ against the control

These experiments were performed on male and female albino rats (190 to 230 g) anaesthetized with urethane (11200 mg/kg, i.p.), and after 2% calcium chloride solution administration to animal foot vein ECG was registered in II standard lead.

In order to test 3-(2,2,2-trimethylhydrazinium)propionate and γ–butyrobetaine pharmaceutical composition usefulness in the prophylaxis and/or treatment of myocardium infarction we examined how effectively it protects myocardium from ischaemia- and reperfusion-induced rhythm disturbances and heart stop because literature cites that γ–butyrobetaine causes heart stop in diastole (W.Linneweh, Z.Physiol.Chem..42, 181, 1929).

Table 6

3-(2,2,2-Trimethylhydrazinium)propionate (M), γ-butyrobetaine (GBB) and their combination effect on ischaemia- and reperfusion-induced heart rhythm disturbances in rats in the therapeutic regimen

Substance	Total dose, mg/kg	Rhythm disturbances (the number of animals from total numb)			ST rise during occlusion (mV)
		Ventricular tachycardy	Ventricular fibrillation	Lethality	
M	50 (25 -injection + 25 - infusion)	10/10	8/10	3/10	0.4±0.1
GBB	50 (25 -injection + 25 - infusion)	7/10	4/10*	1/10*	0.23±0.05*
M+GBB	50 + 50 (25 + 25 - injection and 25 + 25 - infusion)	8/10	5/10*	0/10*	0.20±0.04*
Control		15/15	15/15	7/15	0.44±0.08

* $p<0.05$

The experiments were carried out on Wistar rats (260-330 g). During phenobarbital anaesthesia (50 mg/kg, i.p.) and artificial respiration their chest was opened and the left coronary artery was ligated with 6.0 Silk Ethicon thread which was pulled out through plastic pipe. Occlusion was made by pressing the plastic pipe to the heart surface, and ischaemia stage was controlled by ECG, fixing ischaemia-induced changes in ECG. Solutions of the substances or saline were i.v. injected in two regimens:

1) prophylactically - 30 min before occlusion by administration of 50 mg/kg,

2) therapeutically - 1.5 min after occlusion by administering 25 mg/kg in injection and 25 mg/kg infusively. Infusion was stopped 2 min after reperfusion.

The experiments exhibited that γ–butyrobetaine in the therapeutically regimen during infusion effectively protects myocardium from ischaemia-reperfusion-induced myocardium damages and ventricular fibrillations which are partially resumed after infusion termination (Table 6). On the contrary, γ–butyrobetaine is ineffective in the prophylactic regimen (Table 7).

Table 7

3-(2,2,2-Trimethylhydrazinium)propionate (M), γ-butyrobetaine (GBB) and their combination effect on ischaemia- and reperfusion-induced heart rhythm disturbances in rats in the prophylactic regimen

Substance	Total dose, mg/kg	Rhythm disturbances (the number of animals from total numb)			ST rise during occlusion (mV)
		Ventricular tachycardy	Ventricular fibrillation	Lethality	
M	50 (proph.)	7/8	5/8	2/8	0.31*
GBB	50 (proph.)	8/8	6/8	3/8	0.36
M+GBB	50+50 (proph.)	7/10	5/10*	1/10*	0.27*
Control		15/15	15/15	7/15	0.44

* $p<0.05$

The efficacy of 3-(2,2,2-trimethylhydrazinium)propionate in the therapeutic regimen on this model is relatively low (Table 6). Its action is markedly better in the case of prophylaxis, i.e. 30 min before occlusion when it protects myocardium from ischaemia increase during occlusion (Table 7).

On the other hand, 3-(2,2,2-trimethylhydrazinium)propionate and γ–butyrobetaine containing pharmaceutical composition effectively protects myocardium from ischaemia-reperfusion-induced rhythm disturbances both in the prophylactic and therapeutic regimens (Tables 6 and 7).

Thus, we managed to discover that the pharmaceutical composition containing 3-(2,2,2-trimethylhydrazinium)propionate and γ–butyrobetaine combination possesses a wide spectrum of cardiovascular action which is connected with its effect on blood vessel and myocardium tonus, blood flow as well as cardiac rhythm including myocardium infarction.

Hence, the pharmaceutical composition containing 3-(2,2,2-trimethyl-hydrazinium)propionate and γ–butyrobetaine is promising for the treatment of heart-blood vessel diseases, the efficacy of which is higher against every separate substance.

In the case the active substances are administered as an injection or drops, syrup or drink orally the pharmaceutical composition contains 3-(2,2,2-trimethylhydrazinium)propionate and γ–butyrobetaine in the total amount of 0.5 to 40% by weight, and as a pharmaceutical acceptable solvent - distilled water, saline, glucose or buffer solution.

In the case the active substances are administered as tablets, caplets, dragee, granules, powders or capsules they contain 3-(2,2,2-trimethylhydrazinium)-

propionate and γ–butyrobetaine in the total amount of 0.1 to 0.5 g in a tablet, caplet, dragee, capsule or one portion of powder or granule.

In the case the active substances are administrated transcutaneously their content in an ointment or plaster makes up 0.5 - 40% by weight.

In the case the active substances are administrated rectally their content in a suppository or microenema accounts for 0.5 to 40% by weight.

CLAIMS

1. A pharmaceutical composition for the treatment of cardiovascular diseases, which contains 3-(2,2,2-trimethylhydrazinium)propionate and γ–butyrobetaine composition by weight of 0.5-95 % as an active principle and pharmaceutically acceptable carrier.

2. A pharmaceutical composition according to Claim 1, wherein the ratio of the mentioned substances in the composition is within 1:10, preferably 1:3 to 3:1.

3. A pharmaceutical composition according to Claim 1or 2, wherein it is intended for oral or sublingual administration and is in the form of tablets (with or without a cover), capsules, caplets, dragees, granules, powder or solution, which contain 0.01- 0.5g of active principle by weight in every tablet, capsule, dragee, granule or powder dose, or also as a 0.5-40% solution or syrup for oral administration.

4. A pharmaceutical composition according to Claim 3, wherein the acceptable carrier is selected from the group of substances which consist of stearinic acid and its salts, lactose, glucose, saccharose, starch, talc,

vegetable oils, polyethylene glycols, microcrystalline cellulose, aerosil, aromatizers, flavoring agents, colorants, ethyl alcohol and water, which are taken separately or are used in combinations.

5. A pharmaceutical composition according to Claim 1or 2, wherein it is meant for parenteral administration and it is in a solution form for injections, which contain 0.5- 40% of the active principle by weight and pharmaceutically acceptable solvent.

6. A pharmaceutical composition according to Claim 5, wherein a pharmaceutically acceptable solvent is selected from the group of solvents which contain a distilled water, isotonic solution, buffer solution or glucose solution, which are taken separately or are used in combinations.

7. A pharmaceutical composition according to Claim 1or 2, wherein it is intended for transcutaneous administration of the active principle and it is in the form of ointment, solution or plaster, which contain 0.5-40% of the active principle by weight and pharmaceutically acceptable carrier.

8. A pharmaceutical composition according to Claim 7, wherein the pharmaceutically acceptable carrier is chosen from the group which consist of water, polyethylene glycols 400, 1500 and 4000, vegetable oils, fats, glycerine, preservants, emulgators, stabilisers, porous polymer material, dilnethylsulphoxide, alcohol and water which are taken separately or are used in combinations.

9. A pharmaceutical composition according to Claim 1or 2, wherein it is meant for rectal administration of the active principle in the form of suppositories or microenema, which contain 0.5-40% of the active principle by weight and pharmaceutically acceptable carrier.

10. A pharmaceutically composition according to Claim 9, wherein the pharmaceutically acceptable carrier is selected from the groups which consist of water, polyethylene glycols 400, 1500 and 4000, vegetable oils, fats, glycerine, preservants, emulgators and stabilisers, which are taken separately or used in combinations.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,4 451 485 (KALVINSH IVARS Y ET AL) 29 May 1984 see column 2, line 4-52; claims 1-4 --- -/--	1,3,5,6

[X] Further documents are listed in the continuation of box C.

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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 105, no. 15, 13 October 1986 Columbus, Ohio, US; abstract no. 127077, "Effect of a new structural analog of gamma-butyrobetain, 3-(2,2,2-trimethylhydrazinium)propionate, on carnitine levels, carnitine-dependent fatty acid oxidation and some indexes of energy metabolism in myocardium" XP002022373 see abstract & VOPR. MED. KHIM., vol. 32, no. 4, 1986, page 72-76 SIMKHOVICH ET AL: see page 72-76 ---	1
A	GB,A,2 091 101 (SIGMA TAU IND FARMACEUTI) 28 July 1982 see claims 1,4,6 -----	1,3,5

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/LV 96/00002

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US-A-4451485	29-05-84	DE-A-	3234537	07-04-83
		FR-A-	2512671	18-03-83
		GB-A,B	2105992	07-04-83
		JP-C-	1363933	09-02-87
		JP-A-	58074606	06-05-83
		JP-B-	61029927	10-07-86
GB-A-2091101	28-07-82	AU-A-	7908781	15-07-82
		BE-A-	891639	16-04-82
		CH-A-	649218	15-05-85
		DE-A-	3200016	12-08-82
		FR-A-	2497510	09-07-82
		JP-C-	1738989	26-02-93
		JP-B-	4024325	24-04-92
		JP-A-	57136516	23-08-82
		LU-A-	83869	07-05-82
		NL-A-	8200022	02-08-82
		SE-B-	453569	15-02-88
		SE-A-	8200007	07-07-82
		US-A-	4382092	03-05-83